

PRELIMINARY PROGRAM
ASBMB Fall Symposium
Subcellular Targeting of Signal Transduction Enzymes
October 11-14, 1996
Park City, Utah

October 11 (Friday)

Evening: ***Opening Lecture***

 Tony Pawson, FRS
 Samuel Lunenfeld Research Institute

October 12 (Saturday)

Morning: ***Compartmentalization of Multienzyme complexes***
 Chair: John Scott, Vollum Institute, Oregon Health Sciences University

 Invited speakers
 Ann Marie Pendergast, Duke University
 Beverly Errede, University of North Carolina

Afternoon: ***Poster sessions***

 Special lecture: Susan Taylor, UCSD

Evening ***Targeting of kinases***
 Chair: Susan Jaken, Alton Jones Cell Science Center

 Invited speakers
 G. Stanley McKnight, University of Washington
 Daria Mochly-Rosen, Stanford University

October 13 (Sunday)

Morning: ***Structural Motifs for Subcellular Targeting***
 Chair: Susan Taylor, University of California, San Diego

 Invited speakers
 Brian Hemmings, FMI, Basel
 Stephen Sprang, University of Texas, Southwestern Medical Center

Afternoon: ***From the Membrane to the Nucleus***
 Chair: Roger Tsien, University of California, San Diego.

 Invited speakers
 Lee Limbird, Vanderbilt University
 Richard Goodman, Vollum Institute, Oregon Health Sciences University

October 14 (Monday)

Morning: ***Membrane Translocation***
 Chair, Alexandra Newton, University of California, San Diego

 Invited speakers
 Jim Clarke, Genetics Institute
 Carolyn Buser, SUNY Stonybrook
 Claudia Kent, University of Michigan
 Alan Aderem, University of Washington

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October 11-14, 1996
Subcellular Targeting of Signal Transduction Enzymes

Intracellular transduction of signals from the plasma membrane to specific subcellular compartments is a complex and highly regulated process that controls a myriad of essential cellular events. Perhaps the most graphic demonstration of how signal transduction pathways are essential to maintain cellular homeostasis is the overwhelming evidence that most transforming oncogenes encode signal transduction components such as low molecular weight G-proteins, protein kinases or phosphatases. Furthermore, it is becoming apparent that upwards of 20% of the genome encodes signal transduction components. Now that many of these genes have been identified, the challenge facing researchers is to figure out how these enzymes interface to control cellular events. Not surprisingly, regulation of signal transduction pathways is a sophisticated process that is achieved on many levels. A critical element in this process is the subcellular location of each signal transduction component [Newton 1995].

One emerging mechanism is that the subcellular distribution of several kinases and phosphatases is restricted by association with targeting proteins or subunits [Mochley-Rosen 1995]. A variation on this theme is the formation of kinase/phosphatase signaling complexes to modulate the phosphorylation state of specific target substrates [Faux and Scott 1996]. For example, the action of many tyrosine kinases (PTKs) and tyrosine phosphatases (PTPases) is coupled to downstream cytoplasmic enzymes through adapter proteins that contain SH2 and SH3 domains [Pawson 1995]. Modular proteins like Grb2, p85, IRS-1, Crk and Nck consist of a single SH2 domain that recognizes certain phosphotyrosyl residues on signaling enzymes, and two SH3 domains that bind to a PXXP motif on a separate set of target proteins including cytoskeletal components, enzymes involved in phospholipid metabolism or small molecular weight G-proteins [Pawson 1995]. Similarly, the targeting of many phospholipases, kinases, phosphatases and heterotrimeric G-proteins is mediated by specific membrane-targeting motifs such as the C2, pleckstrin homology and lipid-anchoring domains. Through these interactions signaling complexes are formed which generally emanate from receptor kinases or scaffold proteins and mediate cellular processes including growth factor signaling events, insulin action and immune cell function [Harrison and Errede 1995].

A flurry of recent advances from a variety of laboratories indicate that this is a prime time to evaluate the role of subcellular targeting in the regulation of signal transduction pathways. Accordingly, this meeting will focus on the proteins and structural motifs that function to target signal transduction components. The presentations will range from structural analysis of protein targeting motifs to the use of sophisticated functional assays and genetic techniques to identify novel targeting components. The symposium will open with a lecture from Dr. Tony Pawson, FRS, who has conducted many of the pioneering studies on src homology domains and the modular adapter proteins. The five scientific sessions will cover: compartmentalization of multienzyme complexes, targeting of kinases, structural motifs for subcellular targeting, signal transduction from the membrane to the nucleus, and membrane translocation. Each session will be chaired by individuals who have made seminal contributions to the field and will feature six speakers. The majority of the speakers will be selected from the abstracts. Participation of women and minorities will be encouraged.

In keeping with the spirit of the ASBMB Fall Symposia every effort will be made to encourage the participation of younger investigators, students and postdoctoral fellows. As part of this process, four of the speaking slots in each session will be filled by topics selected from the abstracts. There is no doubt that both of the organizers will positively discriminate toward young investigators as Drs. Newton and Scott were newcomers who benefited tremendously from the opportunity to participate in the 1992 ASBMB Fall Symposium on Protein Kinases and Phosphatases.

Justification and Aims

The current proposal is designed to stimulate focused interaction between scientists studying the subcellular targeting of signal transduction components. Recent advances exemplify the importance of such targeting in diverse systems and for a variety of signal transduction pathways. As examples: scaffolding proteins function to localize protein cascades proteins in yeast, and membrane-targeting motifs regulate the function of many transduction proteins in mammalian cells. A spectrum of experimental strategies ranging from genetic screens to biochemical, cell biological, and biophysical approaches have been applied to understanding the role of subcellular targeting. The goal of the proposed meeting is to bring together a diverse group of investigators that will converge on the view that subcellular localization is a key determinant in the specificity of signal transduction events.

PRELIMINARY PROGRAM

FRIDAY EVENING

The opening lecture will be delivered by Dr. Tony Pawson of the Samuel Lunenfeld Research Institute, Toronto. Dr. Pawson has performed much of the pioneering work on the control of tyrosine phosphorylation events through modular adapter proteins that contain SH2 and SH3 domains. Dr. Pawson's participation in the symposia is particularly appropriate since 1996 is the 10th anniversary of his discovery that SH2 domains are subcellular targeting motifs.

SATURDAY MORNING

Compartmentalization of Multienzyme Complexes

Chair: Dr. John Scott, Vollum Institute

This session will focus on the role of modular adapter proteins that serve as 1) the nucleation sites for multienzyme complexes that emanate from protein tyrosine kinases and 2) multivalent scaffold and anchoring proteins that localize serine/threonine kinase and phosphatase units. The invited speakers will be Dr. Ann Marie Pendergast, Duke University and Dr. Beverly Errede, University of North Carolina. Potential laboratories that may contribute to the session include those of Cantley, Parsons, Brugge, Schlessenger, Brautigan and Mumby.

SATURDAY AFTERNOON

Poster sessions

Special lecture: Dr. Susan Taylor

A special lecture will be given by Dr. Susan S. Taylor, University of California San Diego, on the structure and function of the cAMP dependent protein kinase. Over the years, Dr. Taylor's laboratory has made seminal contributions to our understanding of the structure and function of the cAMP-dependent protein kinase, PKA. In the late seventies and early eighties, Dr. Taylor's group used biochemical and molecular approaches to identify key residues in the kinase. These findings were confirmed when her group solved the crystal structure of the catalytic subunit in 1991 and the regulatory subunit in 1995. Through her efforts PKA is considered the prototypic protein kinase. More recently her work has focused on the subcellular location of PKA and its heat-stable inhibitor PKI. Dr. Taylor's contribution to this symposium will be more than just scientific, as the current president of ASBMB she is an exemplary role model for younger scientists.

SATURDAY EVENING

Targeting of kinases

Chair: Dr. Susan Jaken, Alton Jones Cell Science Center

The goal of this session is to emphasize the recent progress on the subcellular targeting of protein kinases through association with anchoring proteins and targeting subunits. The invited speakers will be Dr. G. Stanley McKnight, University of Washington and Dr. Daria Mochley-Rosen, Stanford University. Potential laboratories that may contribute to the session include those of Rubin, Colbran, Cohen, DePaoli, Aderem and Gallatin.

SUNDAY MORNING

Structural Motifs for Subcellular Targeting

Chair: Dr. Susan Taylor, University of California, San Diego

This session will focus on the structural biology of subcellular targeting motifs. This will include lectures on structural analysis of C2, SH2, and pleckstrin homology domains. The invited speakers will include Dr. Steve Sprang (C2 domain), PH domain (from a company Ask ACN), SH2 domain (Ariadne). Potential laboratories that may contribute to the session include those of Kuryan, Jennings and ICOS corporation.

SUNDAY AFTERNOON

From the Membrane to the Nucleus

Chair: Dr. Roger Tsien, University of California, San Diego.

The concept of this session is to provide a session which emphasizes the contribution of subcellular targeting on the function of various transduction molecules. This will include discussion of basolateral vs. apical targeting of G-protein linked receptors by Dr. Lee Limbird, Vanderbilt University to the formation of the nuclear CREB transcription complex through association with CREB-binding protein from Dr. Richard Goodman, Vollum Institute. Potential laboratories that may contribute to the session include those of Hamm, Morrison and Karin.

MONDAY MORNING

Membrane Translocation

Chair, Dr. Alexandra Newton, University of California, San Diego

The goal of this session is to discuss the role of membrane translocation in signal transduction events and the function of targeting sequences that localize signaling enzymes close to membranes and cytoskeleton. The invited speakers will be Dr. Jim Clarke, (Genetics Institute) and Dr. Stuart McLaughlin, SUNY Stony Brook, Dr. Claudia Kent, University of Michigan, and Dr. Brian Hemmings, FMI Basel. Potential laboratories that may contribute to the session include those of Lefcowitz, Aderem, Nairn, and Valee.

REFERENCES

- Faux, M.C., and Scott, J.D. (1996) Molecular glue: kinase anchoring and scaffold proteins. *Cell* (in press)
- Levin, D.E., and Errede, B. (1995) The proliferation of map kinase signaling pathways in yeast. *Current Opinion in Cell Biology* 7:197-202.
- Mochly-Rosen, D. (1995) Localization of protein kinases by anchoring proteins: a theme in signal transduction. *Science* 268:247-51.
- Newton, A.C. (1995) Protein kinase C: structure, function, and regulation. *J. Biol. Chem.* 278: 28495-28498.
- Pawson, A. (1995) Protein modules and signaling networks. *Nature* 373:573-580.